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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 32

Application Number: 08/716531
Filing Date: September 19, 1996
Appellant(s): Mahe et al

Robin Teskin
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 8/2/00.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

*(3) **Status of Claims***

The statement of the status of the claims contained in the brief is correct.

*(4) **Status of Amendments After Final***

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

*(5) **Summary of Invention***

The summary of invention contained in the brief is correct.

*(6) **Issues***

The appellant's statement of the issues in the brief is correct.

*(7) **Grouping of Claims***

The rejection of claims 1-11 and 16-19 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

*(8) **Claims Appealed***

The copy of the appealed claims contained in the Appendix to the brief is correct.

*(9) **Prior Art of Record***

The following is a listing of the prior art of record relied upon in the rejection of

claims under appeal.

5389615	FERREIRA et al	2-1995
5157023	LIPTON	10-1992
4874744	NORDLUND et al	10-1989

Oluyomi, A. O. "Antinociceptive activity of peptides related to interleukin-1beta-(193-195), Lys-Pro-Thr." European Journal of Pharmacology, vol. 258, (1994), pp. 131-138.

Mullins, J. D. "Medicated Applications." Remington's Pharmaceutical Sciences, 16th Edition. (1980), Chapter 87.

Sciarra, J. J. "Aerosols." Remington's Pharmaceutical Sciences, 16th Edition. (1980), Chapter 92.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

1. Claims 1-3 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ferreira et al or Oluyomi et al.

Ferreira et al disclose the use of a tripeptide K(D)PV and biological equivalents thereof in pharmaceutically acceptable formulations to treat pain (inflammation) (col. 2, lines 46-52, lines 59-61, col. 3, lines 53-59, col. 4, line 59 to coll. 5, line 3 and all the Examples and claims).

Oluyomi et al disclose the use of the K(D)PV and biological equivalents thereof in pharmaceutically acceptable formulations to treat pain (abstract, p. 134-135 and Tables 2-3).

Claim Rejections - 35 USC § 103

2. Claims 4, 7-10 and 18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al as applied to claims 1-3 above.

This reference discloses the use of tripeptides as medicaments to treat or prevent pain wherein said tripeptides are of the formula X-Pro-Y (formula I) where X can be lys or arg and Y can be any amino acid (col. 1, lines 30-50) where the preferred compounds are X=lys or D-lys (col. 2, line 22) and Y=valine (col. 2, line 31) and each of these amino acids can be in its D-form (col. 2, lines 13-17). The preferred form of pro is also D (col. 2, lines 15-17). These compounds read on the tripeptides and functional equivalents thereof of claims 1-4.

The only difference between that and the instant invention is the specific use of D-lys-Dpro-Dval and the combination of another known anti-inflammatory agent with the tripeptides.

As discussed above, the reference clearly suggests the making and the use of Dlys-Dpro-Dval (preferred embodiment). Therefore, in view of this suggestion, it would have been obvious to one of ordinary skill in the art at the time of the invention to make

and use D-lys-Dpro-Dval to treat pain. The combination of two or more known agents to treat a disease is within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art.

3. Claims 5-6 and 19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al as applied to claims 1-3 above further in view of Lipton and Oluyomi et al.

The primary reference discloses the use of tripeptides of IL-1beta as medicaments to treat or prevent pain wherein said tripeptides are of the formula X-Pro-Y (formula I) where X can be lys or arg and Y can be any amino acid (col. 1, lines 30-50) where the preferred compounds are X=lys or D-lys (col. 2, line 22) and Y=valine (col. 2, line 31) and each of these amino acids can be in its D-form (col. 2, lines 13-17). The preferred form of pro is also D (col. 2, lines 15-17).

The only difference between that and the instant invention is the use of protecting groups.

Lipton disclose the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active than the unprotected form (col. 4, lines 58-68).

Therefore, in view of the enhanced activity of the protected peptide over the unprotected peptide, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a protecting groups, such as acetyl, to protect the tripeptides of the primary reference to confer stability to the tripeptides. It is noted that the tripeptides of the primary and secondary references are related (see Oluyomi et al p. 131 which discloses that amino acids 193-1954 of IL-1beta are KPV and that amino acids 11-13 of alpha MSH are KPV and that there peptides are related).

4. Claims 1-11 and 16-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al in view of Nordlund et al, Lipton and Remington's Pharmaceutical Science Ch 87 and 92 and Oluyomi et al.

Ferreira et al disclose the use of tripeptides of IL-1beta as medicaments to treat or prevent pain wherein said tripeptides are of the formula X-Pro-Y (formula I) where X can be lys or arg and Y can be any amino acid (col. 1, lines 30-50) where the preferred compounds are X=lys or D-lys (col. 2, line 22) and Y=valine (col. 2, line 31) and each of these amino acids can be in its D-form (col. 2, lines 13-17). The preferred form of pro is also D (col. 2, lines 15-17). These compounds read on the tripeptides and functional equivalents thereof of claims 1-4. Also see col. 2, lines 46-52, lines 59-61, col. 3, lines 53-59, col. 4, line 59 to col. 5, line 3 and all the Examples and claims.

The only difference between the instant invention and the reference is (1) the use of the tripeptide in a topical formulation, (2) the use of a protecting group, (3) the specific mention of Dlys-Dpro-Dval and (4) the combination of another known anti-inflammatory agent with the tripeptides.

As discussed above, the primary reference clearly suggests the making and use of D-lys-Dpro-Dval (preferred embodiment).

Lipton disclose the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active than the unprotected form (col.. 4, lines 58-68).

Nordlund discloses that alpha MSH can be applied topically to treat inflammatory skin diseases such as dermatitis in a concentration of 10-2M/cm2 to 10-10M.cms (abstract, col. 1, lines 5-41, summary of the invention, col. 2, lines 33-65). The pharmaceutical formulation includes ointments and creams (col.. 2, lines 50-55). Remington's is cited to show that formulation of topical treatments and aerosols is well known in the art.

Therefore, in view of the suggestion of the primary reference to make and use D-lys-D-pro-D-val, it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use D-lys-D-pro-Dval to treat pain. It also would have

been obvious to one of ordinary skill in the art to use a protecting groups, such as acetyl, to protect the tripeptides of the primary reference to confer stability to the tripeptides. It is noted that the tripeptides of the primary reference and secondary references are both derived from amino acids 11-13 of alpha MSH. It also would have been obvious to use the tripeptides of the primary reference to treat inflammatory disorders of the skin and to make formulations suitable for topical administration because according to Nordlund et al MSH is used to treat such disorders and the tripeptides of the primary reference are amino acids 11-13 of MSH (see Oluyomi et al p. 131 which discloses that amino acids 193-195 of Il-1beta and that amino acids 11-13 of alpha MSH are KPV and that these peptides are related). The combination of two or more known agents to treat a disease is within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art.

5. Claims 1-3, 5-11 and 16-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Oluyomi et al in view of Nordlund et al, Lipton and Remington's Pharmaceutical Science Ch 87 and 92.

Oluyomi et al disclose the use of the K(D)PV and biological equivalents thereof in pharmaceutically acceptable formulations to treat pain (abstract, p. 134-135 and Tables 2-3). This reference also discloses that amino acids 193-195 of Il-1beta and that amino acids 11-13 of alpha MSH are KPV and that these peptides are related.

The only difference between the instant invention and the reference is (1) the use of the tripeptide in a topical formulation, (2) the use of a protecting group and (3) the combination of another known anti-inflammatory agent with eh tripeptides.

Lipton disclose the use of protected peptides (specifically acetyl-KPV) and that the use of protected peptides is preferred because the protection group can confer stability to the peptide by decreasing the problems of enzymatic attack and degradation and also discloses that the protected tripeptide is more active than the unprotected form (col.. 4, lines 58-68).

Nordlund discloses that alpha MSH can be applied topically to treat inflammatory skin diseases such as dermatitis in a concentration of 10-2M/cm2 to 10-10M.cms (abstract, col. 1, lines 5-41, summary of the invention, col. 2, lines 33-65). The pharmaceutical formulation includes ointments and creams (col.. 2, lines 50-55). Remington's is cited to show that formulation of topical treatments and aerosols is well known in the art.

In view of Lipton, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a protecting group, such as acetyl, to protect the tripeptides of the primary reference to confer stability. It is noted that the tripeptides of the primary reference and secondary references are related. It also would have been obvious to use the tripeptides of the primary reference to treat inflammatory disorders of the skin and to make formulations suitable for topical administration because

according to Nordlund et al MSH is used to treat such disorders and the tripeptides of the primary reference are amino acids 11-13 of MSH. The combination of two or more known agents to treat a disease is within the purview of one skilled in the art. Dosages are within the purview of one skilled in the art.

(11) Response to Argument

Response to arguments pertaining to the rejection of claims 1-3 under 35 U.S.C. 102(b) as being anticipated by Ferreira et al

Appellant argues that the reference is directed to the treatment of pain not inflammation. The Examiner disagrees. In col. 1, lines 10-30, the reference discloses that IL-1beta is involved in a number of inflammatory disease and that a number of the peptides have been discovered that antagonize such activities (the discovered peptides are analgesics). The reference goes on to state that lys-D-pro-val antagonizes hyperanalgesia (col.. 4, line 29) (ie that the peptide is an analgesic). It is also noted that the reference compares the analgesic activity of the tripeptide to the analgesic activity of indomethacin and indomethacin is a known anti-inflammatory agent. Furthermore, as stated by applicant, "swelling, pain, redness and warmth are the terms which may be used to describe localized inflammation (background of the specification). The it is the reference and the state of the art which equates pain and inflammation.

Appellant further argues that in a 1/15/98 reply, appellant cited pages from a textbook showing that drugs for treating pain are often distinct from drugs that treat inflammation. A careful look at the Table cited by appellant shows that 2 drugs out of 18 listed only treated one disorder. Thus, 16 out of 18 drugs (about 89%) tested treated both inflammation and pain.

Appellant argues that Hoffman and Schmelz (abstract only), which they submitted during prosecution shows that inflammatory mediators responsible for vasodilation are not identical with those inducing hyperalgesia. Even though hyperalgesia and inflammation may be caused by different stimuli, it is clear that from the state of the art that pain is part of inflammation (see above) and as evidenced by appellants own reference (table discussed in the previous paragraph), the drugs that treat pain also treat inflammation.

Appellant argues that a method for treating inflammation would not overlap with a method for treating pain. Appellant goes on to quote pages 1-2 of the specification which states "localized inflammation is associated with swelling, pain, redness and warmth". Thus, pain is part of inflammation and again, as evidenced by appellants own reference (table discussed in the previous two paragraph), the drugs that treat pain also treat inflammation.

Appellant argues that they submitted a declaration by Mahe stating that it was is opinion that a compound which inhibits pain would not reasonable inhibit inflammation. For all of the above reason, the Examiner disagrees with the declaration.

Response to arguments pertaining to the rejection of claims 1-3 under 35 U.S.C. 102(b) as being anticipated by Oluyomi et al.

Appellant argues that the reference teaches away from the instant because the pro must be in the L form for activity and appellant argues that Oluyomi and Hiltz must be read together. First of all, appellant is simply ignoring the data presented in the Oluyomi reference. The reference compares the activity of indomethacin to the tripeptide and as stated above, indomethacin is a well known anti-inflammatory agent. The reference further states that the peptide analogs containing the dipeptide lys-pro "constitute a novel approach to the control of pain, particularly **inflammatory** pain "(emphasis added, p. 131 second column, first full paragraph). The reference state that the peptide inhibits the release of prostaglandin and other inflammatory agents (p. 136, first column, lines 5-9 from the bottom) and additionally on page 137, first column, lines 8-11 that "this confirms the peripheral anti-inflammatory activity of this peptide' (this peptide refers to lys-D-pro-val). Thus, the reference is dealing with the treatment of inflammation.

Second, in response to appellant's arguments that the Hiltz et al reference only shows that the L-Pro form is active, the Examiner provides the following. While the reference does state this, applicant is requested to carefully analyze both references together. First of all, applicant is NOT claiming the NH2 form of the peptide. Secondly, the reference is a 1991 reference and the Oluyomi et al reference, which is a 1994 reference, clearly shows that lys-D-pro-valNH2 is effective in the **late phase** (see page 137 (col. 1, lines 6-8)). It is not clear which phase of inflammation Hiltz et al is referring to when they say that it is inactive. Since there are several phases of inflammation and since it is not clear if both references were testing activity in the same phase and since Oluyomi et al is a 1994 reference which clearly shows activity in the late phase, absent objective evidence to the contrary, the Oluyomi et al reference supersedes the Hiltz et al reference. Appellant is also directed to the last sentence on page 137 which states that "**We conclude that useful analgesics may be developed from peptides containing the sequence Lys-*D-Pro*-X"**(emphasis added). Thus, the 1994 reference does show and believe that peptides containing D-pro are anti-inflammatory.

Appellant argues that the reference uses tests conventional for measuring pain--the reference uses a rat paw test (which the Examiner assumes to be the formalin test). The formalin test described on page 132 is a test for inflammation--this is supported by page 136, second column, which discusses the release of inflammatory mediators in

response to formalin and thus, the drugs tested treat the release of inflammatory mediators--thus, the reference again shows that inflammatory pain is discussed.

Response to arguments pertaining to the rejection of claims 4, 7-10 and 18 under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al as applied to claims 1-3 above.

Appellant relies on the arguments set forth and rebutted above.

Response to arguments pertaining to the rejection of claims 5-6 and 19 under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al as applied to claims 1-3 above further in view of Lipton and Oluyomi et al.

With respect to Ferriera et al and Oluyomi et al, appellants relies on the arguments set forth above. These arguments have been addressed above.

With respect to the Lipton reference, appellant argues that the reference does not teach peptides with the D from of pro. As discussed in the rejection, this reference was cited to show that the use of protection groups to increase stability is well known in the art and that it is the combination of the two references which makes appellants invention obvious.

Response to arguments pertaining to the rejection of claims 1-11 and 16-19 under 35 U.S.C. 103(a) as being unpatentable over Ferreira et al in view of Nordlund et al, Lipton and Remington's Pharmaceutical Science Ch 87 and 92 and Oluyomi et al.

With respect to Ferriera et al and Oluyomi et al and Lipton, appellant relies on the arguments set forth above. These arguments have been addressed above.

With respect to Nordlund and Remington's, appellants argue that the reference do not cure the deficiencies cited in Ferreira and Oluyomi. As discussed above, the Examiner believes that there as no deficiencies in either Ferreira et al or Oluyomi. Nordlund and Remington's were cited merely to shows that topical administration is obvious and it is the combination of the references which makes appellants invention obvious.

Response to arguments pertaining to the rejection of claims 1-3, 5-11 and 16-19 under 35 U.S.C. 103(a) as being unpatentable over Oluyomi et al in view of Nordlund et al, Lipton and Remington's Pharmaceutical Science Ch 87 and 92.

Appellant's arguments have been address above.

(12) For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

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